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Renal hemodynamics during pregnancy in chronically catheterized, conscious rats

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Renal hemodynamics during pregnancy in chronically catheterized, conscious rats. Two types of experiments were performed, cross-sectional and longitudinal. In the cross-sectional studies, rats were mated, later prepared surgically, and then 5 or more days after surgery, each examined twice during days 11 to 15 or days 18 to 20 of gestation. Nonpregnant rats matched for age and prepregnant weight served as controls. In the longitudinal studies, rats were catheterized and, starting 6 days later, examined twice; then the same rats were mated and each was studied on days 5, 8, 12, 16, and 20 of gestation, as well as on day 5 postpartum. In the cross-sectional studies, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were elevated by approximately 26% and 20%, respectively, above nonpregnant controls at 11 to 15 days of gestation (GFR, 2739 ± 94 vs. 2181 ± 134 $\mu l \cdot min^{-1}$, $P < 0.005$; ERPF, 9367 ± 295 vs. 7785 ± 422 $\mu l \cdot min^{-1}$, $P < 0.01$). By 18 to 20 days of gestation, GFR and ERPF had returned to levels that were not significantly different from nonpregnant values. The longitudinal studies confirmed these findings in every respect and further revealed that GFR and ERPF were elevated above nonpregnant values as early as day 5 of gestation ($P < 0.005$). Thereafter, they rose to peak values, at 12 and 16 days of gestation, of 3122 ± 144 and 10,584 ± 541 $\mu l \cdot min^{-1}$, and then returned to nonpregnant levels by day 20 of gestation. Because these changes in GFR and ERPF resemble those of human pregnancy, the chronically prepared, conscious, pregnant rat can serve as a useful model in which to investigate the mechanisms underlying the changes.

Hémodynamique rénale pendant la gravidité chez des rattes éveillées, avec un cathéter chronique. Deux types d'expériences ont été entrepris: *(1) Transversales.* Des rattes ont été fécondées, préparées ensuite chirurgicalement, puis 5 jours ou plus après la chirurgie, chacune a été examinée deux fois aux jours 11 à 15 et 18 à 20 de la gestation. *(2) Longitudinales.* Les rattes étaient cathétérisées, puis, au bout de 6 jours, examinées deux fois; ensuite les mêmes rattes étaient fécondées, et chacune était étudiée aux jours 5, 8, 12, 16, et 20 de la gestation, ainsi qu'au 5e jour du post-partum. Dans les études transversales, le débit de filtration glomérulaire (GFR) et le débit plasmatique rénal efficace (ERPF) étaient élevés de 26% et 20% environ, respectivement, au-dessus des contrôles non gravides, à 11 à 15 jours de gestation (GFR, 2739 ± 94 contre 2181 ± 134 $\mu l \cdot min^{-1}$, $P < 0{,}005$; ERPF, 9367 ± 295 contre 7785 ± 422 $\mu l \cdot min^{-1}$, $P < 0{,}01$). A 18 à 20 jours de gestation, GFR et ERPF étaient revenus à des niveaux non significativement différents des valeurs non gravides. Les études longitudinales ont confirmé ces résultats dans leur entier, et ont en plus révélé que GFR et ERPF étaient élevés au-dessus des valeurs non gravides dès le 5e jour de gestation ($P < 0{,}005$). Ensuite ils s'élevaient à des valeurs maximum aux 12e et 16e jour de gestation de 3122 ± 144 et 10584 ± 541 $\mu l \cdot min^{-1}$, puis revenaient aux niveaux non gravides au 20e jour de gestation. Puisque ces modifications de GFR et ERPF ressemblent à celles de la grossesse humaine, la ratte gravide, préparée de façon chronique et éveillée peut servir de modèle utile pour chercher les mécanismes sous-jacents à ces modifications.

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A summary of the data obtained from pregnant rats reveals disagreement on whether changes occur in glomerular filtration rate and renal plasma flow (Table 1). This disagreement may arise in part because the rats were subjected to different types and doses of anesthetics or to varying degrees of surgical maneuvers, which, of themselves, perturb renal hemodynamics [1–3]. Moreover, plasma volume, which can fall during surgery [4] and influence renal hemodynamics [5], was often not assessed for this possibility, nor was it restored to normal levels; on the other hand, frequently, excess fluids were administered. These confounding variables may have obscured any physiologic changes in renal hemodynamics that might have occurred during pregnancy. This consideration is particularly apropos, since pregnancy represents a radically altered physiologic state; it is not inconceivable that a pregnant individual may respond differently than a nonpregnant "control" to comparable doses of anesthetics, degrees of surgical stress, and changes of plasma volume.

To circumvent the influence of anesthesia, acute surgery, and alterations of plasma volume, the present study used trained, chronically catheterized, conscious rats [6]. The purpose, then, was to develop an experimental animal preparation in which one could study renal function during pregnancy in a relatively undisturbed state, and to ascertain to what extent renal function during pregnancy in the rat resembles that in the human. The successful development of this animal model will now enable us to further investigate the mechanisms that underlie changes in renal hemodynamics during pregnancy.

Methods

Animal preparation. Long-Evans rats (Charles River, North Wilmington, MA) fed a normal diet (Charles River RMH 3000 formula) were used. Body weights are listed under **Results.** All animals underwent training in the experimental cage [6] prior to surgery (2 hours a day for at least 5 days). Details of the surgical preparation, including the construction and implantation of vascular catheters and bladder cannulae, have been previously described [6].

In brief, under ketamine (60 mg · kg of body wt^{-1}) and pentobarbital (7.0 mg · kg of body wt^{-1}) anesthesia, rats under-

Table 1. Renal hemodynamics during rat pregnancy[a]

Reported effect	Days of gestation[b]		
	5 to 7	9 to 16	17 to 22
A. Significant increase in GFR and/or RPF[c]	22, 27, 33	22, 24, 27, 30, 33, 35, 37	22, 28, 32, 33, 35, 36, 39, 41
B. No significant change in GFR and/or RPF	31	28, 32, 36	27, 38, 40

[a] Numbers cited in table refer to references.
[b] Days of gestation have been arbitrarily divided to span early, mid, and late pregnancy.
[c] GFR is glomerular filtration rate; RPF, renal plasma flow. Many investigators reported ERPF (effective renal plasma flow), rather than RPF.

went left femoral artery and vein cannulation with Tygon catheters (Norton, Akron, OH). The tips of these catheters lay, respectively, in the abdominal aorta and inferior vena cava below the renal arteries and veins. Both catheters were exteriorized between the scapulae. A cannula of silastic-covered stainless steel was then sewn into the urinary bladder with a purse-string suture, and exteriorized through the ventral abdominal wall. The catheters were filled with a heparin-dextrose mixture and plugged with a straight pin; the bladder cannula was stoppered with a silastic-covered 18-gauge pin.

Experimental procedures. After surgical preparation, each rat underwent routine postoperative care as described by Gellai and Valtin [6] except that antibiotics were not administered. Five to seven days were allowed for recovery, by which time rats were gaining weight and appeared healthy.

Two types of experiments were performed, cross-sectional and longitudinal. In the cross-sectional experiments, rats were initially mated, later surgically prepared, and then studied either on gestation days 11 to 15 ($N = 7$ animals) or on days 18 to 20 ($N = 7$ different animals); rats of the same age and prepregnant weight served as nonpregnant controls ($N = 5$ and 10 animals, respectively). (Rat gestation is 22 days.) Each rat was usually studied twice at either gestational period, with 48 hours of rest between studies. Pregnancy was confirmed afterwards by sacrificing the animals or allowing them to deliver.

In the longitudinal experiments, 11 rats were initially catheterized by an aseptic technique and studied twice prior to conception with at least 48 hours of rest between studies. Because of difficulty with the bladder cannulae in 2 of these rats, only 9 animals were used in the studies of renal function. The vascular catheters were then allowed to slip beneath the skin so that the male rat could not disturb them during the mating period. The rats were mated (conception was documented by the presence of spermatozoa in the vaginal lavage, designated as day 1 of gestation), and within the next 24 to 48 hours the catheters were re-exteriorized under ether anesthesia. Studies were conducted in the same rat on gestational days 5, 8, 12, 16, and 20. Within 8 hours following delivery (day 22), the pups were counted, weighed, and then sacrificed. Rats were last studied on postpartum day 5.

Details of the experimental procedure for both types of protocol were as follows. A rat was placed in the experimental cage. A special cage was designed to accommodate the enlarging abdominal girth of rats during gestational days 16 to 20; they were placed in this larger cage if their weight exceeded 310 to 320 g. The femoral arterial catheter was connected to a Statham pressure transducer (Statham Instrument Div., Hato Rey, PR) and Grass polygraph (model 5D, Quincy, MA) for monitoring of mean arterial pressure (MAP). Blood samples were obtained from this catheter. The femoral venous catheter was attached to a Sage variable infusion pump (Orion Research, Inc., model 355, Cambridge, MA) for the delivery of polyfructosan (Inutest, Laevosan-Gesellschaft, Linz-Donau, Austria) and PAH (sodium aminohippurate, Merck, Sharp and Dohme, West Point, PA) in Ringer's solution. Finally, the bladder cannula was extended with a polyethylene tube (Intramedic, Clay Adams, Parsippany, NJ), and timed urine collections were made, under oil. Urine volume was measured gravimetrically. The clearances of polyfructosan and PAH provided a measure of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively.

After the infusion was started (10% polyfructosan and 0.75 or 1% PAH in Ringer's solution at 10 $\mu l \cdot min^{-1} \cdot 100$ g of body wt^{-1}), an equilibration period of at least 45 min was allowed. Then two 30-minute renal clearances were obtained with midpoint blood samples (each sample, approx. 250 μl). The red cells were resuspended in Ringer's solution and returned to the rat.

Analytical techniques. Polyfructosan in plasma and urine was determined by the anthrone method [7]; and PAH, by the method of Bratten and Marshall as modified by Smith et al [8]. Sodium and potassium in plasma and urine were measured by flame photometry (model 343, IL, Inc., Lexington, MA), and plasma and urine osmolality were assessed by a vapor pressure osmometer (Wescor, Inc., 5100C, Logan, UT).

All data have been expressed per whole animal. The unpaired or paired Student's t tests were used to assess the statistical significance of any observed differences.

Results

At 11 to 15 days' gestation. Nonpregnant (9 observations in 5 animals) and pregnant rats of 11 to 15 days' gestation (13 observations in 7 animals) were of comparable *starting* weight (253 ± 7, 252 ± 9 g) and age (88 ± 2, 90 ± 2 days). At the time of study, the nonpregnant rats weighed 258 ± 7 g; and the pregnant ones, 287 ± 7 g ($P < 0.01$). Because they were studied concurrently, their ages during the studies were similar (103 ± 1, 105 ± 2 days).

Table 2 shows that, on average, the rats at 11 to 15 days of gestation demonstrated a significant elevation in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), by approximately 26% ($P < 0.005$) and 20% ($P < 0.01$), respectively. The "effective" filtration fraction did not change significantly. A significant decline in mean arterial pressure (MAP; $P < 0.02$) was apparent at this gestational period (Table 2); this decline, in conjunction with a rise in ERBF, resulted in a "renal vascular resistance" (RVR), which was significantly decreased ($P < 0.005$; *see* calculation in Table 2).

Table 2. Renal hemodynamics in nonpregnant and pregnant rats at gestational days 11 to 15 and 18 to 20

	Nonpregnant	*P*	11 to 15 days	Nonpregnant	*P*	18 to 20 days
No. of observs.; no. of rats	9; 5		13; 7	20; 10		13; 7
Mean arterial pressure, *mm Hg*	104 ± 1	< 0.02	99 ± 2	109 ± 2	NS	107 ± 2
Glomerular filtration rate, $\mu l \cdot min^{-1}$	2181 ± 134	< 0.005	2739 ± 94	2409 ± 70	NS	2462 ± 78
Effective renal plasma flow, $\mu l \cdot min^{-1}$	7785 ± 422	< 0.01	9367 ± 295	7893 ± 246	NS	7242 ± 344
"Effective" filtration fraction[a]	0.28 ± 0.01	NS	0.29 ± 0.01	0.31 ± 0.01	< 0.001	0.35 ± 0.01
"Renal vascular resistance,"[b] $mm\ Hg/ml \cdot min^{-1}$	7.82 ± 0.37	< 0.005	6.28 ± 0.24	7.96 ± 0.26	< 0.02	9.12 ± 0.38

[a] Calculated as GFR/ERPF.
[b] Calculated as MAP-5/ERBF.

At 18 to 20 days' gestation. Nonpregnant (20 observations in 10 animals) and pregnant rats of 18 to 20 days' gestation (13 observations in 7 animals) were again of comparable starting weight (248 ± 5, 254 ± 8 g) and age (97 ± 2, 100 ± 3 days). At the time of study, the nonpregnant rats weighed 250 ± 5 g; and the pregnant ones, 320 ± 7 g ($P < 0.001$). Because they were studied concurrently, their ages during the study were similar (118 ± 2, 121 ± 3 days).

Table 2 shows that GFR, ERPF, and MAP were not significantly different by this late stage of gestation. Because the ERPF, however, tended to be lower in pregnant rats, the "effective" filtration fraction was higher ($P < 0.001$). The hematocrit was further decreased at this gestational period (36.6 ± 0.6 vs. 41.3 ± 0.3, $P < 0.001$), which in combination with a somewhat lower ERPF actually resulted in a significant elevation of RVR ($P < 0.02$; *see* calculation in Table 2).

Longitudinal studies. On average, the body weight of the animals immediately prior to surgery was not significantly different from that during the initial studies 6 days later (248 ± 4 vs. 242 ± 4 g, respectively; $P > 0.1$). The rats were recovering their body weights, and were healthy by the time of experimentation. After conception, their weight increased at each gestational period examined ($P < 0.001$ for all periods when compared with the initial, nonpregnant mean) such that by day 20, pregnant rats were on average approximately 40% above their nonpregnant weight. With only one exception, all rats delivered a normal number of pups. (In Figs. 1 and 2, the number of animals that were studied after day 12 of gestation decreases because a cannula had ceased functioning, not because animals had died.) The mean litter size for all animals was 11 ± 1. In addition, the weight per newborn pup was 6.0 ± 0.2 g. These values are comparable to those reported by Charles River for their Long-Evans breeders. Finally, upon close inspection, no congenital deformity was displayed by any of the newborn.

Figure 1, A and B, portrays the GFR and the ERPF for the 9 individual rats (as well as the means) whose renal function was followed throughout gestation. On average, both GFR and ERPF were significantly elevated above nonpregnant values, as early as day 5 ($P < 0.005$). They continued to increase, achieving peak values at midgestation of 3122 ± 144 and 10,548 ± 541 $\mu l \cdot min^{-1}$, respectively. These levels represent a 25 to 30% increase over the nonpregnant values of 2439 ± 110 and 8226 ± 297 $\mu l \cdot min^{-1}$ ($P < 0.001$ and < 0.005, respectively). By day 20 of gestation, however, GFR and ERPF had returned to nonpregnant levels. "Effective" filtration fraction was approximately 0.30 in the nonpregnant and pregnant states until day 20, when it rose to 0.35 ± 0.02 ($P = 0.07$).

Fig. 1C indicates that there was a significant fall in RVR as early as day 5 of gestation ($P < 0.01$), when compared to the nonpregnant mean. A nadir of 5.86 ± 0.35 mm Hg/ml · min^{-1} occurred by midgestation, a value significantly less than the mean of 7.63 ± 0.35 mm Hg/ml · min^{-1}, which the same rats showed prior to conception ($P < 0.001$). By day 20 of gestation, the RVR had returned to the nonpregnant value.

Mean arterial pressures (MAP) for the individual rats studied longitudinally are presented in Fig. 2. MAP significantly decreased, by 4 to 5 mm Hg, on day 12 ($P < 0.02$). Although the MAP remained below nonpregnant values throughout the remainder of gestation, the points were not statistically different from the nonpregnant mean.

In general, the filtered load and absolute net reabsorption of sodium, potassium, osmoles, and water were all significantly increased during gestation except on day 20, when they returned toward the nonpregnant values (not shown). The fractional reabsorption of solutes at various stages of gestation was decreased significantly, but only to a small degree, such that the increase in excretion of solutes and water was minimal. For example, in the nonpregnant state, urinary excretion of sodium was 2.1 ± 0.4 μEq · min^{-1}; on day 12 of gestation, when the filtered load of sodium had increased by as much as 80 μEq · min^{-1}, sodium excretion rose slightly to 4.3 ± 0.4 μEq · min^{-1} ($P < 0.005$). Additional variables are presented in Table 3. Notably, plasma sodium concentration was significantly decreased as early as day 5; it declined continuously thoughout the remainder of gestation. Plasma osmolality, however, did not fall until day 12. The osmolality listed for day 12 was not significantly different from the nonpregnant mean; if, however, one spuriously low value of 262 mOsm/kg H_2O on day 12 were deleted, the new difference would become statistically significant (290.1 ± 0.8 vs. 293.5 ± 0.6 mOsm · kg H_2O^{-1}, $P < 0.02$). Also beginning with day 12 of gestation, the hematocrit declined from control values.

Discussion

The application of a chronically prepared, conscious animal preparation to the study of renal hemodynamics during pregnancy provides at least four distinct advantages: *(1)* The perturbations of renal hemodynamics and of the hormonal and cardiovascular systems, which are brought about by anesthesia and surgical stress [1–3, 9–16], as well as by alterations of plasma volume [4, 5], are circumvented. *(2)* Each animal can

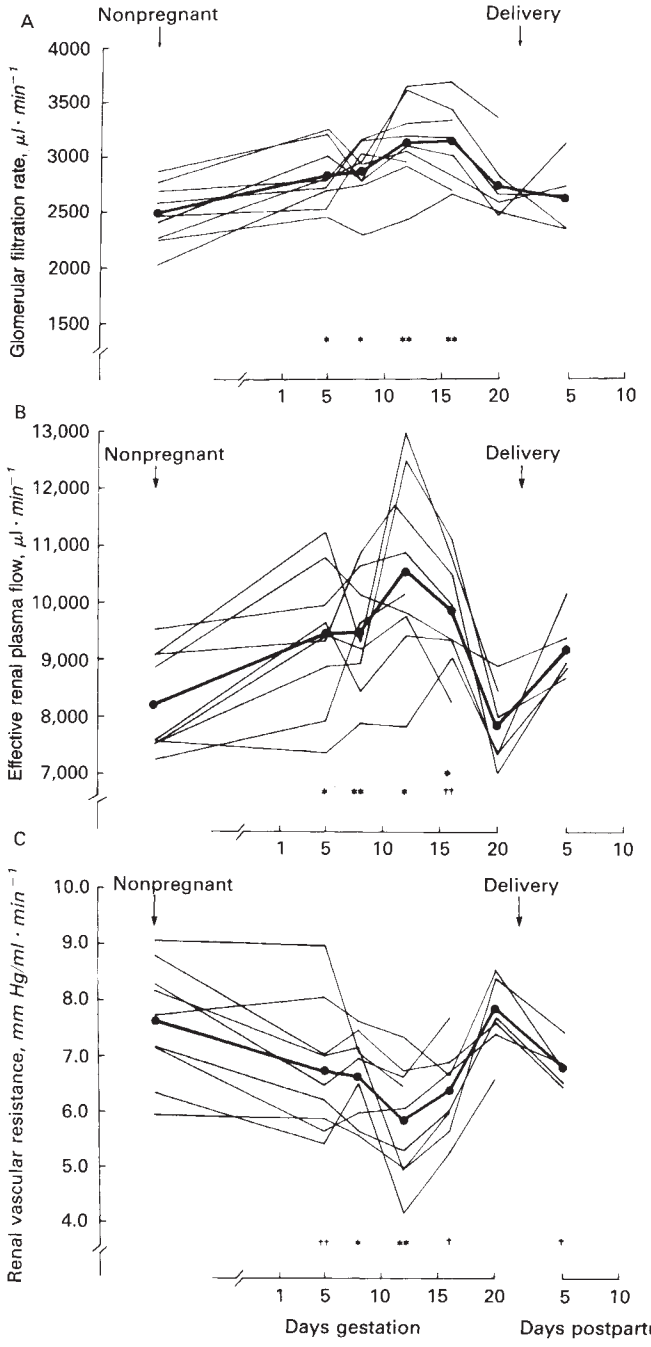

Fig. 1. *Individual values of GFR, ERPF, and RVR ("renal vascular resistance," calculated as MAP−5/ERBF) for the rats studied longitudinally before, during, and after gestation.* Mean values are denoted by the filled circles that are connected by the heavy line. †$P < 0.05$, ‡$P < 0.01$, *$P < 0.005$, **$P < 0.001$ from the nonpregnant mean.

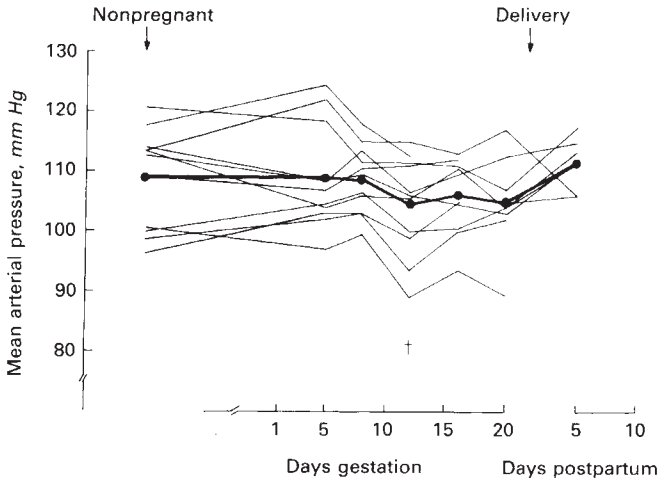

Fig. 2. *Individual values of MAP for the rats studied longitudinally before, during, and after gestation.* Mean values are denoted by the filled circles that are connected by the heavy line. †$P < 0.05$ from the nonpregnant mean.

serve as her own control; that is, the same animal can be studied longitudinally—before, during, and after pregnancy. *(3)* A priori, data obtained from conscious and undisturbed, rather than anesthetized, acutely prepared animals would seem to be more comparable to data obtained from human pregnancy. *(4)* Inasmuch as the data obtained in the present model resemble those of human pregnancy (see below), it is possible that future results regarding mechanisms can be extrapolated to humans.

The major finding of the present study is that despite differences between rat and human pregnancies, changes that occur in the renal hemodynamics of both species are remarkably similar. As did humans [17–19], so did conscious rats demonstrate a significant rise in GFR and ERPF during early gestation (gestational day 5, $P < 0.005$; Fig. 1, A and B). This elevation became more pronounced by midgestation whether the pregnant rats were compared with nonpregnant controls in a cross-sectional study (days 11 to 15, Table 2), or examined longitudinally (days 12 to 16, Fig. 1, A and B), in which each animal served as her own control. Although the maximal rise of renal hemodynamics attained during midgestation in rats (25 to 30%) may not be as great as that seen in humans (40 to 60% [17–19]), the peak occurs at a similar stage of pregnancy in both species. Finally, in cross-sectional (Table 2) and longitudinal (Fig. 1, A and B) studies, renal hemodynamics returned to nonpregnant values by days 18 to 20 of gestation. Interestingly, this decline in renal hemodynamics during late gestation occurred in the face of further expansion of plasma volume, as indicated in our study by the additional decrement of hematocrit on gestational days 18 to 20 (*see* **Results** and Table 3). Although most studies of human pregnancy have demonstrated that renal hemodynamics remain elevated by late gestation, there is a decline from the peak levels of midgestation [17–19]. Thus, in general, the changes of renal hemodynamics in the trained, chronically prepared, conscious pregnant rat mimicked those of human gestation.

The present study also suggests that MAP falls during pregnancy in the rat. This decline was significant during midgestation (Table 2 and Fig. 2). In the cross-sectional studies (Table 2), there was no difference in MAP between pregnant and nonpregnant animals at term. These data seem to conflict with the longitudinal studies (Fig. 2) in which MAP may have been decreased throughout the latter half of gestation, although the changes were not significantly different after day 12. Because of the variability of blood pressure even within individual ani-

Table 3. Other characteristics in rats studied longitudinally before, during and after gestation[a]

		Gestation					
	Nonpregnant	day 5	day 8	day 12	day 16	day 20	Postpartum[b]
Urine flow rate, $\mu l \cdot min^{-1}$	27.6 ± 3.4 (9)	31.5 ± 5.4 (9)	35.8 ± 3.1†† (9)	39.2 ± 6.4 (9)	33.6 ± 3.2 (7)	33.0 ± 4.9 (6)	30.5 ± 3.2 (5)
Plasma Na^+, $mEq \cdot liter^{-1}$	141.1 ± 0.4 (11)	139.4 ± 0.7† (11)	139.5 ± 0.5† (11)	138.4 ± 0.5** (11)	136.8 ± 0.4** (9)	136.0 ± 1.3* (9)	141.5 ± 0.8 (7)
Plasma osmolality, mOsm · kg H_2O^{-1}	293.5 ± 0.6 (11)	294.3 ± 1.0 (11)	296.4 ± 1.2 (11)	287.6 ± 2.6 (11)	286.4 ± 1.4** (9)	282.6 ± 1.6** (9)	297.6 ± 1.2† (7)
Plasma K^+, $mEq \cdot liter^{-1}$	4.6 ± 0.1 (11)	4.7 ± 0.1 (11)	4.8 ± 0.1 (11)	4.8 ± 0.1 (11)	4.8 ± 0.1 (9)	4.7 ± 0.1 (9)	4.6 ± 0.1 (7)
Hematocrit, %	41.0 ± 0.5 (11)	39.6 ± 0.9 (11)	40.1 ± 0.6 (11)	39.3 ± 0.5† (11)	39.8 ± 1.0 (8)	37.3 ± 1.0† (9)	43.1 ± 1.0 (7)

[a] Values are the means ± SEM. Numbers in parentheses represent the number of rats. Symbols denote statistical significance: †$P < 0.05$, ††$P < 0.01$, *$P < 0.005$, **$P < 0.001$ from nonpregnant values.

[b] Day 5.

mals, it would be necessary to study more rats, preferably in a longitudinal fashion to firmly establish the course of MAP during pregnancy. Other studies in acutely prepared rats have shown a decrease in MAP only at term [22], or no change at all throughout gestation [21]. In one study [20], rats with chronically indwelling arterial catheters were examined; the animals displayed a fall in MAP 2 days before delivery, but measurements were only made from day 15 onwards. Values obtained by tail-sphygmometry throughout gestation demonstrated a fall near term [20]. The longitudinal studies presented here do not disagree with published data; MAP tended to be lower during late gestation, although it was not significant. The present data do suggest that the decline in MAP may occur earlier in rat pregnancy than previously thought—as early as day 12 (at least in the Long-Evans strain).

A significant fall in hematocrit was noted by midpregnancy in the cross-sectional ($P < 0.005$) and longitudinal studies (Table 3), which declined even further thereafter. This decline is a consistent finding for rat (for example, [23, 24]) and human [25] pregnancy, and it occurs despite an increase in red cell mass (at least in human pregnancy [25]), apparently in the face of an even greater increase in extracellular and plasma volumes [23, 25–27]. This increase in extracellular and plasma volume resulted in only a small increment in solute and water excretion; large increases in the filtered load of substances were nearly matched by increases in absolute net reabsorption. Last, an early decline in plasma sodium concentration (Table 3) confirms previous findings in rats [23, 24, 28] and humans [29]. This decline preceded that of plasma osmolality (Table 3), an observation previously reported by Atherton et al [23]. The plasma osmolality decreased by midgestation, and declined further thereafter, in parallel with sodium concentration.

The data on renal hemodynamics confirm several previous studies, but dispute others (see Table 1). They agree, in part, with data from Baylis, in which euvolemic, Munich-Wistar rats prepared for micropuncture, were studied on gestation days 9 [30] and 12 [24]. On the other hand, the data presented in the present study show a significant, early rise in renal hemodynamics (Figs. 1A and B), which was not demonstrated by Baylis [31]. The studies of Atherton and Pirie, performed in anesthetized, acutely prepared rats infused with isotonic saline at 37.5 $\mu l \cdot min^{-1}$, agree with the present study, in that GFR (plasma flow was not assessed) was significantly elevated during early and mid, but not late gestation [27]. (Since these authors designate conception as day 0 rather than day 1 of pregnancy, the earliest, significant rise in GFR in their study occurred on days 6 to 7 by my method of dating.) Atherton recently published a study in conscious rats [22], but whether these rats were free of stress is uncertain. For example, it is not clear how long the rats were allowed to recover following implantation of arterial and venous catheters. Also, because bladder cannulae were not implanted, it is not certain how micturition was initiated. Nevertheless, data from the study support the earlier work by this group in the anesthetized preparation [27], except that a significant elevation in GFR persisted during late gestation. The exhaustive studies by Lindheimer and Katz in anesthetized rats [28], and by Davison and Lindheimer in unanesthetized, acutely prepared rats (several hours postimplantation of catheters under ether [32]), revealed a significant rise in GFR (not ERPF) only during late gestation (18 to 20 days), which disagrees with the present study. It is possible that the surgical stress present in their unanesthetized rat preparation may have obscured some of the changes in renal hemodynamics [3]. Studies by Garland and Green [33] in rats prepared for micropuncture, are similar to the present study, except that they noted a significant elevation of GFR on day 19 (plasma flow was not assessed); this elevation, however, was lower than that observed on day 12. In a more recent study [40], the same investigators failed to show any difference in GFR between virgin and 19-day pregnant rats.

In summary, a survey of the literature (Table 1) shows considerable controversy, which may have arisen, at least partly, from the variable effects upon renal hemodynamics of different types and doses of anesthetics, varying degrees of surgical stress and alterations of plasma volume, as well as potential variations that may exist among different strains of rats. Nevertheless, the present study, performed in conscious, undisturbed rats, does confirm several others carried out in different rat strains and preparations.

The mechanisms that underlie the alterations in renal hemodynamics during pregnancy are unknown. Hormones may be responsible, as endocrine status is altered dramatically during

pregnancy. For example, Elkarib, Garland, and Green have suggested that prolactin may contribute toward the rise seen during early gestation in the rat [34]. Further investigations are required to define the mechanisms involved. The trained, chronically prepared, conscious, pregnant rat would seem to be an ideal model in which to pursue these further investigations.

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